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Human Epididymis Protein 4 Predicts Progressive Interstitial Fibrosis and Adverse Cardiovascular Events in Patients with Dilated Cardiomyopathy

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Background: Cardiac fibrosis plays a crucial role in the pathogenesis of dilated cardiomyopathy (DCM). Human Epididymis Protein 4 (HE-4) is a secretory protein expressed in activated fibroblasts and inhibits matrix metalloproteinase-mediated collagen degradation. However, its role in DCM is largely unknown.

Methods: We measured serum HE-4 levels of 87 patients with DCM and followed their echocardiographic parameters and cardiovascular events. *In vitro,* HE-4 plasmid was introduced into Human embryonic kidney cells (HEK) 293T. The culture supernatant was transferred to previously harvested rat neonatal cardiomyocytes and cardiac fibroblasts.

Results: Masson`s trichrome staining of endomyocardial biopsy revealed significantly greater fibrosis in the high than low HE-4 group (<59.65 pmol/L [median value]). The echocardiography showed that left ventricular end-diastolic diameter (LVEDD) was significantly decreased over time (58±7.3 to 51±6.6 mm, $p<0.0001$) in the low HE-4 group, with no inter-group differences at baseline. HE-4 was an independent determinant for mortality and cardiovascular hospitalization in multivariate Cox model (hazard ratio: 5.85, 95%CI: 2.77-12.35, $p<0.0001$). HE-4 was highly expressed in kidney tissue of adult mice, and scarcely expressed in the heart, indicating that one of the main sources of circulating HE-4 is kidney tissue. The supernatant from HE-4 transfected HEK293T cells enhanced transdifferentiation of fibroblasts and deposition of extracellular matrix proteins, and was accompanied by the activation of ERK signaling in cardiac fibroblasts.

Conclusions

HE-4 functions as a secretory factor activating cardiac fibroblasts, thereby inducing cardiac interstitial fibrosis. HE-4 could be an unconventional biomarker for assessing ongoing fibrosis and a novel therapeutic target in DCM.